Remarks

The Specification

Incorporation by reference

The specification is objected to as having improperly incorporated documents by reference. Applicant respectfully traverses the objection. The instant application is a continuation of USSN 09/070,497, which was a continuation of USSN 07/949,652, now issued U.S. Patent No. 5,612,179 ("the '179 patent"). The specification as filed was identical to the specification of the issued '179 patent. Applicant submits that as the specification of the issued '179 patent was found to be non-objectionable, the incorporations by reference in the instant specification should also be non-objectionable.

According to MPEP §2163.07(b), "Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter."

The Action states that, "To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates by reference and clearly indicated where that material is to be found in the various documents." (citing *Advanced Display Systems, Inc. vs. Kent State University*, 54 USPQ2d at 1679 (Fed Cir. 2000)) Applicant notes that the instant application does indicate with detailed particularity what specific material it incorporates by reference and where that material is to be found in the various documents. Specifically, the instant specification explicitly states that each of the cited references "is incorporated herein by reference in its entirety." In other words, the specific material incorporated by reference is the entire content of each cited document, and the material is to be found in the entire text of each such document.

The Action provides no authority for the position that it is impermissible to incorporate by reference the contents of an entire document. The recitation in MPEP §2163.07(b) to the incorporation by reference of "the content of another document or part thereof" makes clear that

an entire document may properly be incorporated by reference. As the instant application states with detailed particularity that the entire content of each of the cited documents is incorporated by reference, and it is clear that the entire contents of the documents are to be found in the entire text of each document, Applicant submits that the specification is unobjectionable for its incorporation by reference. Applicant points out that in the cited case of *Advanced Display Systems, Inc. vs. Kent State University*, the Federal Circuit did not find improper any incorporation by reference, either in whole or in part.

Applicant notes that numerous recently issued U.S. patents have continued the practice of incorporating documents by reference in their entirety. For example, U.S. Patent No. 6,615,048 states that, "All patents, patent applications, documents, standards, protocols, and draft protocols referred to herein are incorporated herein by this reference in their entirety." It therefore cannot be the general policy of the USPTO to prohibit incorporation by reference of documents in their entirety. If it is the policy of the USPTO to prohibit incorporation by reference of documents in their entirety, Applicant requests that the Examiner identify the relevant section of the MPEP where such policy is set forth. In the absence of such identification, Applicant submits that the instant application is proper in its incorporation by reference.

Declaration

The Action objects to the Inventor's Declaration on the grounds that, "the pending claim(s) no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claim(s)." Applicant notes that claims 31-46 are canceled herein. Of the pending claims, claims 2, 3, 5-7, 12, 14, 15, 17, 18, 20 and 21 are original. As discussed below, pending claims 1, 8, 9, 11, 13, 19, 23 and 25-30 find ample support in the Specification as filed and in the original claims. Applicant respectfully asserts that the presently pending claims substantially embrace the invention as set forth in the statement of the invention and/or in the original claim(s), obviating the requirement for a supplemental oath or declaration.

It is unclear in what manner the claims are asserted to no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claims. Applicant notes that the title of the instant application as filed was, "Intron sequence analysis method for detection of adjacent and remote locus alleles as haplotypes." The Summary of the Invention states that:

The present invention provides a method for detection of at least one allele of a genetic locus and can be used to provide direct determination of the haplotype. The method comprises amplifying genomic DNA with a primer pair that spans an intron sequence and defines a DNA sequence in genetic linkage with an allele to be detected. The primer-defined DNA sequence contains a sufficient number of intron sequence nucleotides to characterize the allele. Genomic DNA is amplified to produce an amplified DNA sequence characteristic of the allele. The amplified Dna sequence is analyzed to detect the presence of a genetic variation in the amplified DNA sequence such as a change in the length of the sequence, gain or loss of a restriction site or substitution of a nucleotide. The variation is characteristic of the allele to be detected.

The present invention is based on the finding that intron sequences contain genetic variations that are characteristic of adjacent and remote alleles on the same chromosome. In particular, DNA sequences that include a sufficient number of intron sequence nucleotides can be used for direct determination of haplotype.

The method can be used to detect alleles of genetic loci for any eukaryotic organism. Of particular interest are loci associated with malignang and nonmalignant monogenic and multigenic disease, and identification of individual organisms or species in both plants and animals. In a preferred embodiment, the method is used to determine HLA allele type and haplotype.

It is unclear to Applicant in what manner the "pending claim(s) no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claims(s)." If the object is maintained, further clarification is requested.

Sequences

The Action objects to the specification as containing "representations of nucleic acids that are not accompanied with the corresponding SEQ ID NO. The amendments to the Specification above address this issue. Applicant notes that SEQ ID NOs 79 through 87 were inadvertently omitted from the original sequence listing filed in this application. A substitute sequence listing and diskette are submitted herewith. Support for the sequences is included in the Specification at least at pg. 83, line 17 and pages 89 through 90. Therefore no new matter is added to the case.

The Claims

Support for Amendments

Claims 1, 8, 13 and 19 have been amended to refer to methods of determining at least one haplotype encompassing a human HLA coding locus. The amendment to the claims is without

prejudice or disclaimer and Applicant reserves the right to prosecute claims of broader scope in a continuation application. Support for the amendment may be found in the Specification at least at pg. 7, lines 9-11 and 24-25; pg. 11, lines 3-9; pg. 14, line 3 through pg. 15, line 26 and pages 42 through 93. Applicant submits that no new matter is added by the amendment.

Written Description

Pending claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicant respectfully traverses the rejection.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. [MPEP 2163.02]

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). [MPEP 2163.02]

Applicant respectfully submits that rejection of the pending claims under 35 U.S.C. 112, first paragraph, for failure to comply with the written description requirement is improper under the Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, ¶1, "Written Description" Requirement (the "Guidelines") [Fed. Register 66(4):1099-1111, 2001], as well as applicable Federal case law. Applicant initially notes that there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed. [*In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976)]. The Guidelines make extensive reference to Federal Circuit decisions such as *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) as examples of applications that did not provide adequate written description support. Applicant respectfully submits that the fact situations presented by such cases were significantly different from the present application and therefore not applicable precedent.

In *Eli Lilly*, 119 F.3d 1559, the claims in question were drawn to a product that was held to be inadequately described. The product in question concerned generic DNA sequences encoding mammalian insulin, while the patent specification only disclosed an exemplary species of DNA encoding rat insulin. In that case, a variety of specific DNA molecules (products) of unknown sequence were encompassed by the claims. The Court held that, under those circumstances, disclosure of the exemplary species did not provide adequate written description support for the generic claim. A similar fact pattern was seen in *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200 (Fed. Cir. 1991), where a patentee had disclosed a method for obtaining a DNA sequence without disclosing the sequence itself. Both cases involved a lack a written description support for claimed DNA sequences that had not been disclosed in the patent applications as filed.

In the instant application there is no product claimed as part of the pending claims. The pending claims recite methods of haplotype determination. Although such methods may result in the determination of one or more nucleic acid sequences, those sequences *per se* are not the subject of the claims. Thus, the cited Federal Circuit decisions finding a lack of written description support for product claims concerning specific nucleic acid sequences are not appropriate precedent for the instant method claims.

The Action acknowledges that, "the specification does provide a description of analyzing the HLS DQA1 locus in humans". Applicant respectfully submits that the disclosure is broader than characterized by the Action. For example, the specification discloses analysis of the $DQw1_v$ alleles of the DQB1 locus at least in Table 3 and pg. 43, last paragraph. Analysis of the DPB4.1, DPB9, New and DPw3 alleles of the DPB1 locus is shown at least in Table 4 and pg. 44, last paragraph. HLA primers for the A locus, B locus and C locus are shown at pages 57-59. Primers for the DRA locus, DRB locus, DQB1 locus and DPB1 locus are shown at pages 62-64. Applicant notes that claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 as amended concern methods of determining at least one haplotype encompassing a human HLA coding locus. Such claims are more than adequately supported by the specification.

The Action asserts that the claims, "have been interpreted as encompassing a method whereby any haplotype in any life form is determined." Applicant notes that the claims as amended concern methods of determining at least one haplotype encompassing a human HLA coding locus. Applicant submits that there is ample written description for claims of such scope. The amendment to the claims is without prejudice or disclaimer and Applicant reserves the right to prosecute claims of broader scope in a continuation application.

The Action also asserts a lack of written description support for use of primers of any length to generate amplicons of any length. The Action cites the Specification for stating that amplicons are to range in size from 800 to 2000 nucleotides, while primers are to range in size from 8 to 30 nucleotides. Applicant respectfully traverses. The specification states at pg. 16, lines 3-12 that, "For example, the least polymorphic HLA locus is DPA which currently has four recognized alleles. For that locus, a primer pair which amplifies only a portion of the variable exon encoding the allelic variation contains sufficient genetic variability to distinguish between the alleles when the primer sites are located in an appropriate region of the variable exon. Exon-limited primers can be used to produce an amplified sequence that includes as few as about 200 nucleotides (nt)." Thus, written description support is found in the specification for amplicons at least as short as 200 nucleotides in length. At pg. 14, lines 31-35 recite that, "About 300 to 500 nucleotides is sufficient, depending on the location of the sequence. That is, 300 to 500 nucleotides comprised primarily of intron sequence nucleotides sufficiently close to the variable exon are sufficient." At pg. 20, lines 12-13 the specification states that, "Preferably, the

amplified DNA sequence is between 300 to 1,000 nt...." At pg. 20, lines 31-35, "For allelic differences detected by ASO or SSO probes, the amplified DNA sequence includes a region of from about 200 to about 400 nt which is present in one or more alleles and not present in one or more other alleles." Thus, written description support is found for amplicons of less than 800 nucleotides in length.

The Action asserts a lack of identification of where support for claims 26-46 may be found. Applicant points to the amendment filed on November 1, 2002, at page 6 for identification of where in the specification support for claims 26-30 may be found. Applicant points to the amendment filed on May 2, 2003, at pages 11-12 as identifying where in the specification support for claims 31-46 may be found. However, cancellation of claims 31-46 obviates the new matter objection to those claims. The cancellation of claims 31-46 is without prejudice or disclaimer and Applicant reserves the right to prosecute the subject matter of those claims in a continuation application. For the convenience of the Examiner, the citation to support for claims 26-30 from the Preliminary Amendment filed on November 1, 2002, is reproduced below.

> The amendment to claims 1, 13 and 19 to recite "genetic coding locus" or "HLA coding locus" is supported in the specification at least at pg. 11, lines 3-9, which defines a "genetic locus" as including a gene that encodes a protein including any upstream or downstream transcribed noncoding regions and associated regulatory regions.
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> The addition of new claims 26 and 29, reciting haplotype determination by detecting polymorphisms in coding and non-coding regions, is supported at least by original claim 12 and by the specification at least at pg. 8, lines 4-6 which recites that "intron sequences provide genetic variations that, in addition to those found in exon sequences, further distinguish sample DNA...." Additionally, pg. 16, lines 13-16 specifies that the amplified sequence to be analyzed "preferably includes at least a portion of one of the introns adjacent to a variable exon and can include a portion of the variable exon. When additional sequence information is required, the amplified DNA sequence preferably encompasses a variable exon and all or a portion of both adjacent intron sequences." At pg. 21, lines 19-24 the specification discloses various types of polymorphisms used to distinguish the haplotypes of the DQA1 locus.
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> The addition of new claims 27, 28 and 30, reciting non-coding regions comprising an intervening sequence, 5'-UTR, 3'-UTR, a regulatory sequence or an intergenic sequence is supported in the specification at least at pg. 9, lines 29-35 which states that the term "intron" refers to untranslated DNA sequences between exons (i.e., intervening sequences), together with 5' and 3' untranslated regions

associated with a genetic locus and intergenic spacing sequences. The new claims are further supported at pg. 10, lines 5-8, which defines an "intervening sequence" and at pg. 15, lines 20-22 which discusses "highly conserved intron regions, e.g., promoters, operators and other DNA regulatory regions."

In consideration of the cited support, Applicant submits that the pending claims introduce no new matter into the disclosure.

Enablement

Pending claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicant respectfully traverses the rejection.

The Action states that, "As presented above, the specification has been found to set forth 8 examples. From these examples, the specification has been found to enable analysis of the human HLA DQA1 locus whereby the allele for cystic fibrosis can be detected. The specification has not been found to set forth a reproducible procedure whereby any haplotype of any life form can be determined, much less identify whether the life form is susceptible to any given disease."

Applicant asserts that the Specification is broader in scope than characterized by the Action. As discussed above, the Examples disclosed in the Specification are not limited to HLA DQA1, but further disclose analysis of the $DQw1_v$ alleles of the DQB1 locus at least in Table 3 and pg. 43, last paragraph. Analysis of the DPB4.1, DPB9, New and DPw3 alleles of the DPB1 locus is shown at least in Table 4 and pg. 44, last paragraph. HLA primers for the A locus, B locus and C locus are shown at pages 57-59. Primers for the DRA locus, DRB locus, DQB1 locus and DPB1 locus are shown at pages 62-64.

The Action further states that, "In order to practice such a method, the skilled artisan would need appropriate starting materials, e.g., primers, as well as conditions under which they are to be used. Seemingly applicant is attempting to avoid disclosing the requisite starting materials by disclosing a general approach to producing primers. While such a disclosure may go towards fulfilling enablement requirements for a method of producing primers, the claimed method is not directed to a method of selecting primers. Rather, one must already have in their possession such essential starting materials, and knowledge of the reaction conditions under which they are to be used."

The Action cites *Genentech v. Novo Nordisk A/S* for the proposition that, "when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill [sic] in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

This case appears to be precisely on point. As stated by the court in *Genentech*, the specification, "must supply the novel aspects of an invention in order to constitute adequate enablement." (emphasis added) However, the Action acknowledges that, "the claimed method is not directed to a method of selecting primers." Nowhere does the instant application assert that methods of selecting primers and conditions of their use are part of the novel aspect of the present invention. Methods of primer selection and hybridization and conditions of amplification were generally known as of the priority date of the instant application. Because such methods were not part of the novel aspect of the present invention, it is not required for enablement purposes that each and every potential primer and conditions for each possible amplication be set forth explicitly in the Specification.

Because the primer sequences and amplification conditions are not part of the novel aspect of the present invention, the knowledge of one skilled in the art may be relied upon. As noted by the Action, information that is known in the art need not be included in a patent specification in order to support enablement. "A patent need not teach, and preferably omits, what is well known in the art." [*In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).]

As noted by the Action, general considerations for primer selection and conditions of hybridization and amplification are disclosed in the instant application, along with exemplary specific primer sequences and hybridization and amplification conditions for a number of representative loci. Numerous specific primer sequences and detailed conditions for hybridization and amplification of chromosomal DNA were explicitly set forth at pages 57-93 of the instant application. Other exemplary specific primer sequences and hybridization and amplification conditions are incorporated by reference into the instant application. Such

disclosure, along with general knowledge in the art, is more than sufficient to enable the full scope of the pending claims. Applicant respectfully submits that the instant Specification provides ample enablement support for the claimed subject matter.

Double Patenting

The claims are provisionally rejected under the judicially created doctrine of double patenting. The Action asserts that the pending claims "are not patentably distinct" from claims 1-7 of U.S. Patent No. 5,192,659 and claims 1-36 of U.S. Patent No. 5,612,179. Applicant is willing to submit a terminal disclaimer in the event that patentable subject matter is found in the instant application.

Conclusion

For the reasons stated above, Applicant submits that all pending claims are in condition for allowance and requests an early decision to that effect. If any remaining issues concerning the allowability of the pending claims remains, Applicant requests the courtesy of a telephonic interview with the Examiner.

Charge our Deposit Account

Please charge any shortage to our Deposit Account No. 02-2666.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR & ZAFMAN LLP

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Richard A. Nakashima
Reg. No. 42,023

12400 Wilshire Boulevard
7th Floor
Los Angeles, California 90025-1030
(303) 740-1980